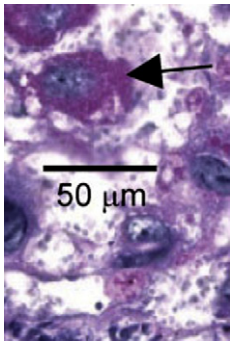
Cell Stem Cell

Editors' Notes

Networking with Oct-4

The fate and function of pluripotent cells are balanced by a complex regulatory network that determines whether ESCs and iPSCs remain pluripotent or differentiate. Doble and colleagues examine *GSK-3*-deficient ESCs and show that β-catenin participates in the switch from pluripotency toward differentiation along the neuroectoderm lineage. They also make the surprising finding that β-catenin can enhance Oct-4 activity without needing to interact with TCF and can, therefore, be considered an independent functional component of the core pluripotency network. Koh and colleagues take an epigenetic approach to investigating the regulation of pluripotency. They focus on the impact of a relatively new epigenetic modification pathway, hydroxylation of methylcytosine mediated by the Tet family of enzymes, on pluripotent cell programming and reprogramming. They find that the role(s) played by Tet1, Tet2, and Tet3 vary across relatively primitive and more differentiated cells and that Tet1 in particular has a strong impact on pluripotent cell fates. Tet enzymes are targets as well as regulators in the pluripotency network, as their expression is in turn also regulated by Oct-4.

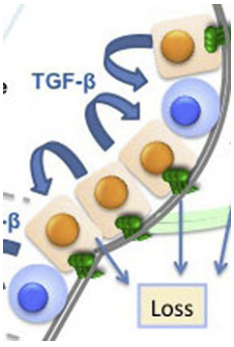


Finding a Desired Heart

To harness the potential of pluripotent cells, the field must continue to develop efficient and robust differentiation protocols for lineages of interest. To this end, Keller and coauthors present a Resource article that applies a specific approach that may also help inform parallel advances for other cell types. In their paper, Kattman et al. derive cardiomyocytes from mouse and human ESCs and iPSCs by using developmental clues to define the optimal concentration and kinetics of Activin/Nodal and BMP signaling agonists. Progression along the cardiac mesoderm lineage can be monitored by following the expression of Flk-1and PdgfR-β. Importantly, different cell lines, even though ostensibly similar, require individual protocol optimization to maximize differentiation potential. As discussed by Tim Kamp in his In Translation article, a growing number of groups have reported patient-derived iPSC lines that can be differentiated to generate mutant, disease-modeling systems, most recently for cardiac arrhythmias such as Long QT Syndromes. Kamp also highlights that the production of specific cardiac lineages offers the potential for drug testing and design, both for the modeled disease, specifically, and also to assay for potential off-target effects of unrelated therapeutic candidates. Both of these articles emphasize the potential uses of human pluripotent cells, but, as Aaron Levine discusses in his Forum article, the ongoing international policy debate over research funding appears to have a strong influence on the specific experimental approaches being adopted, or delayed, by stem cell scientists who work with both pluripotent and adult stem cells, at least in the United States.

Striking Out Cancer

Applying the cancer stem cell model to therapeutic strategies depends on the ability to target the tumor-initiating cells. In this issue, Kuperwasser and colleagues examined sample biopsies from individuals who carry *BRCA1* mutations but have not yet developed cancer. These individuals are particularly prone to aggressive basal-like breast cancer, but the mechanism underlying this tumor propensity remains unclear. By expressing oncogenes in the mutant mammary epithelial samples to initiate cancer, the authors found that BRCA1 mutations promote differentiation toward the basal cell fate and that the transcriptional repressor Slug is a mediator of this BRCA1-dependent bias. This study highlights that fate-determining differentiation pathways could also serve as functionally effective targets for clinical intervention. Another epigenetic modifier, Lsh, has been identified by Mills et al. as a target of a p63 isoform, which works with Ras to overcome senescence in epithelial stem cells and promote tumorigenesis. Many tumor-forming cells and other stem cell populations can be isolated using a flow-cytometry-based method known as the "side population" (SP) assay, which depends on their ability to efflux Hoescht dyes. As Niclou and colleagues describe in their Protocol Review, the SP assay can be a powerful technique for cell enrichment, especially when used in conjunction with surface marker staining. However, it is also a highly sensitive and variable methodology and its successful use depends on the inclusion of consistent controls and rigorous reporting standards.



Tissues with Turnover

External regulatory inputs on stem cell fate and function are often derived from the niche, which can include both cellular and acellular components. Nishimura and coauthors find that hair follicle stem cells (HFSCs) and melanocyte stem cells depend on a specific hemidesmosomal transmembrane collagen molecule, COL17A1, and, in particular, that premature hair graying and loss arises in the absence of this anchoring protein. In this model, the two stem cell populations are inter-related as the HFSCs, which express COL17A1, serve as a niche component for the melanocyte stem cells. Their findings may provide an explanation for the hair loss observed in people with a genetic deficiency in *COL17A1*. Intracellular signals also provide important cues for stem cell function, and Jasper and colleagues use a *Drosophila* model to demonstrate that intracellular redox balance is regulated by Nrf2 and Keap1 to control intestinal stem cell proliferation. In the absence of these two proteins, ROS accumulation accelerates degeneration of the intestinal epithelium, perhaps because of ISC exhaustion. Lessons learned using this model may help inform studies of stem cell homeostatic mechanisms in other high turnover tissues.